Appendix 5: PFA Study Clinical Report

DETERMINATION OF STATIC UVA PROTECTION FACTORS (PFA)

TKL STUDY NO. PB840400

CONDUCTED FOR:

The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241-9974

Attention: J. Frank Nash, PhD

DATE OF DRAFT REPORT:

August 4, 2000
Revised September 1, 2000

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APPENDICES

TITLE OF STUDY

Determination of Static UVA Protection Factors (PFA)

SPONSOR

The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241-9974

Attention: J. Frank Nash, PhD

STUDY MATERIALS

Code B	MF# SWS316-074
Code C	MF# SWS316-076
Code D	MF# SWS316-078
Code E	MF# SWS316-094
Code F	MF# SWS316-096
Code G	MF# SWS316-095
Code I	MF# BCS541-116
Code J	MF# BCS541-118

DATE STUDY INITIATED

April 19, 2000

DATE STUDY COMPLETED

June 17, 2000

DATE OF DRAFT REPORT

August 4, 2000

INVESTIGATIVE PERSONNEL

Alan H. Greenspan, MD
Principal Investigator

Robert C. Reardon, PhD
Director of Operations

Maureen Damstra, BA
Certified Clinical Research Coordinator

Teresita Tadeo, RMA
Supervisor of Photobiology

Maria Sparano, BA
Senior Clinical Assistant

Sharna Green, RMA
Clinical Assistant

CLINICAL SITE

TKL RESEARCH, INC.
4 Forest Avenue
Paramus, NJ 07652

STATEMENT OF QUALITY ASSURANCE

All data and supporting documentation for this study have been audited by the TKL Quality Assurance Department and found to be accurate, complete and in compliance with the requirements of the protocol and TKL's Standard Operating Procedures. This report has been reviewed and accurately reflects all aspects of the conduct of the study.

All clinical research studies are performed by TKL Research, Inc. in accordance with federal regulations and proposed guidelines for good clinical practices which include:

21 CFR Part 312,	Investigational New Drug Application
21 CFR Part 50,	Protection of Human Subjects
21 CFR Part 56,	Institutional Review Boards

_____ _____

Senior Quality Assurance Associate Date

SUMMARY

Product Codes B, C, D, E, F, G, I, and J, were evaluated for UVA Protection Factor (PFA) determination under standard sunscreen study conditions. Twenty-one subjects completed the study, some of whom evaluated more than one product.

Under the conditions employed in this study, the following UVA Protection Factors were obtained:

PRODUCT IDENTIFICATION	EST. PFA	PFA/STD. DEVIATION	NUMBER OF SUBJECTS
B	2-4	3.11 ± 0.44	8
C	3-5	4.91 ± 0.71	8
D	5-7	7.46 ± 1.67	8
E	1-3	1.67 ± 0.41	8
F	1-3	2.41 ± 0.50	8
G	2-4	3.37 ± 0.92	8
I	1-3	2.28 ± 0.47	8
J	2-4	2.93 ± 0.89	8

1.0 INTRODUCTION

1.1 OBJECTIVE

The objective of the study was to determine the static UVA Protection Factor (PFA) for Sunscreen formulas.

1.2 BACKGROUND

Eight products were submitted for evaluation. On the basis of information provided by the Sponsor, these products were considered reasonably safe for evaluation on human subjects.

2.0 STUDY MATERIALS

2.1 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIALS

Upon arrival of the materials used in this study at TKL Research, Inc., receipt was documented in a general log book which serves as a permanent record of the receipt, storage, and disposition of all study materials. At the conclusion of the clinical study, the remaining study materials was discarded or returned to the Sponsor and the disposition documented in the log book. All information regarding the receipt, storage and disposition of the study materials was also recorded on a Clinical Material Record form (see Appendix II) which is incorporated in this study report. All study materials are kept in a locked product storage room accessible to clinical staff members only.

2.2 NATURE OF STUDY MATERIALS

Product Identification	:	Code B MF# SWS316-074
Description	:	off-white lotion
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01
Product Identification	:	Code C MF# SWS316-076
Description	:	off-white lotion
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01
Product Identification	:	Code D MF# SWS316-078
Description	:	off-white lotion
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01

Product Identification	:	Code E MF# SWS316-094
Description	:	white lotion
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01
Product Identification	:	Code F MF# SWS316-096
Description	:	white lotion
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01
Product Identification	:	Code G MF# SWS316-095
Description	:	white lotion
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01
Product Identification	:	Code I MF# BCS541-116
Description	:	white lotion
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01
Product Identification	:	Code J MF# BCS541-118
Description	:	yellowish liquid
Quantity Provided	:	2 x 80 g
Amount Applied	:	0.10 g/50 cm^2
Expiration Date	:	02/01/01

3.0 EXPERIMENTAL DESIGN

This was a controlled, randomized study. Subjects entered into the study had their initials entered sequentially on the Subject Assignment Sheet. The randomization of the application of the study products to the areas of the subject's back were indicated on this sheet.

3.1 STUDY GROUP SELECTION

Each subject was expected to participate in the study for 3 days.

3.1.1 Inclusion Criteria

1. Individuals 18-65 years old were enrolled into the study only after it was determined that each belongs to skin type I, II, or III as defined in the proposed monograph for SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN DRUGS, Federal Register of August 25, 1978 (43FR38206-38269).

2. Individuals free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would interfere with the study results or increase the risk of adverse events.

3. Individuals who completed a photo study Medical Screening form, as well as a Medical/Personal History form.

4. Individuals who read, understood and signed an informed consent agreement.

3.1.2 Exclusion Criteria

1. Medical history not consistent with good general health.

2. History of recent (topical or systemic) use of medication, cosmetic, soap, or fragrance formulations known to produce abnormal sunlight responses.

3. History of severe abnormal responses to sunlight.

4. Individuals with any visible skin disease, excessive hair, blemished, tan or uneven pigmentation at the study site which, in the opinion of the investigative personnel would interfere with the study results.

5. History of chronic use of high doses of antihistamine or anti-inflammatory medications (e.g., aspirin, ibuprofen or corticosteroids) or current use of any antihistamine, NSAID or prescription anti-inflammatory drugs.

6. Individuals taking medication suspected of causing photobiological reactions (e.g. tetracyclines, thiazides).

7. Individuals with psoriasis and/or active atopic dermatitis /eczema.

8. Females who were pregnant, planned to become pregnant during the study, or were breast-feeding a child.

9. Individuals with diabetes, Addison's disease or thyroid conditions.

10. Individuals who were currently under steroidal treatment for asthma, non steroidal treatment is acceptable (e.g., Proventil inhaler).

11. Individuals with cataracts.

12. Individuals with a history of skin cancer.

13. Individuals with a history of hepatitis.

14. Individuals with a known sensitivity to cosmentics, skin care products or topical drugs as related to products being evaluated.

3.1.3 Informed Consent

A properly executed informed consent document in compliance with FDA regulations (21 CFR 50) was obtained from each subject prior to entering the study. The signed informed consent is maintained in the study file. In addition, the subject was provided with a copy of the informed consent. A sample of the consent agreement is included as Appendix IV.

4.0 PROCEDURE

4.1 PRE-STUDY

Before being entered into the study, the subjects were pre-screened by the investigative personnel for the criteria indicated in the Subject Selection section. Only subjects who met the requirements of this section, had signed an informed consent according to 21 CFR, Part 50 and had given an appropriate medical history were entered into this study.

4.2 LIGHT SOURCE

The source of radiation was a Xenon arc solar simulator having a continuous emission spectrum in the UVA (320 to 380 nm) region with less than 1% of its total energy contributed by wavelengths below 320 nm. The lamp was filtered with a WG335 filter, 3mm in thickness or equivalent. There will be less than 2% of erythemal effectiveness of the source contributed from wavelengths lower than 320 nm, and no more than 10% of the total output of the lamp will be visible and infrared radiation. The maximum intensity at the point of the skin exposure must be less than 150 mW/cm^2 total irradiance, as measured by a calibrated thermopile.

4.3 Minimal Response Dose (MRD) Determination

On Day 1 of the study, a minimal response dose (MRD) for unprotected skin was determined for each subject by irradiating 5 one-centimeter subsites on the lower back. The dose interval selected for the irradiation of the subsites was a geometric series wherein each exposure dose interval is 25% greater than the previous exposure.

For subjects of unknown sensitivity, the dose series was in the range of approximately 10 to 31J/cm^2. For subjects with predetermined UVA MRD values, the dose series was centered around the previously determined MRD.

After the exposure is completed, all immediate responses were recorded. These include immediate darkening or tanning, immediate erythema, whealing, edema or flaring at the irradiation site. No subject exhibited whealing, edema or flaring at the irradiation sites.

After the immediate responses were recorded, the subjects were instructed to shield the exposed areas from further UV exposure. Sixteen to 24 hours after the UV exposure, the 5 subsites were graded using the scale indicated in the Clinical Measurements section. The subsite with the lowest exposure dose showing a minimally perceptible tanning or erythema response was selected as the MRD. The unprotected MRD was reconfirmed on the day the test products are evalauted.

4.4 PFA Determination

1. Application of Test Products: Using a permanent marker, each subject had up to six 50cm^2 test areas drawn on the back between the beltline and the shoulder blades and lateral to the midline. Up to five test areas were used for the study products and the remaining one was used for the MRD. Following the randomization indicated on the Subject Assignment Sheet, 100 mg of Sunscreen formula was applied to the appropriate test area and spread over the entire area using a finger cot.

   In the same manner, 100 mg of Sunscreen formulas was applied to the designated test areas. The test areas were allowed to dry for 20 minutes. During this period, the subjects were instructed not to touch their backs against any surface.

2. Irradiation of the Static PFA Test Areas: While the test areas were drying, the solar simulator exposure doses required for Sunscreen formulas were calculated based on the MRD of the subject and the expected PFA value of the sunscreen.

Each 50cm^2 test contained 5 subsites that were irradiated. The dose intervals selected for the subsites were a geometric series in which each exposure doe (subsite) is 25% greater than the previous exposure dose (1.25 x n). For example, if the subject's unprotected MRD is 10 J/cm^2 and the expected PFA of the sunscreen is 2, then the central exposure interval (third subsite) will be 10 X 2 or 20 J/cm^2, respectively.

Sixteen to 24 hours after irradiation, all subsites in the test areas were graded for responses using the scale indicted in the Clinical Measurements section and the PFA values will be determined.

4.5 Study Flow Chart

DAY	ACTIVITIES
1	Obtained informed consent; completed medical screening form; conducted UV irradiation for MRD determination.
2	Determined MRD; calculated UV exposure times; irradiated study product site; untreated site for second MRD determination.
3	Evaluated all sites; calculated PFA.

5.0 PROTOCOL

See Appendix V.

6.0 DATA SUMMARY

See Tables 1 through 8 (Appendix I).

7.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms were designed to identify each subject by subject number and/or subject entry number and, where appropriate, subject's initials, the products evaluated and the reactions observed. Originals or copies of all case report forms, source documents, IRB documents (if required), correspondence, study reports, etc. will be kept on hard-copy file for a minimum of five years from completion of the study. Storage is maintained either at the TKL Research, Inc. facility in a secured room accessible only to TKL employees, or at an offsite location which provides a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of TKL Research, Inc.

8.0 RESULTS & DISCUSSION

Product Codes B, C, D, E, F, G, I, and J, were evaluated for UVA Protection Factor (PFA) determination under standard sunscreen study conditions. A total of 21 subjects between the ages of 18 and 65 were enrolled and completed PFA evaluation of the study products (see Demographics - Appendix III).

PRODUCT IDENTIFICATION	EST. PFA	PFA/STD. DEVIATION	NUMBER OF SUBJECTS
B	2-4	3.11 ± 0.44	8
C	3-5	4.91 ± 0.71	8
D	5-7	7.46 ± 1.67	8
E	1-3	1.67 ± 0.41	8
F	1-3	2.41 ± 0.50	8
G	2-4	3.37 ± 0.92	8
I	1-3	2.28 ± 0.47	8
J	2-4	2.93 ± 0.89	8

9.0 SIGNATURES

Maureen Damstra, BA
Certified Clinical Research Coordinator

Date

Alan H. Greenspan, MD
Principal Investigator

Date

Robert C. Reardon, PhD
Director of Operations

Date

APPENDIX I

TABLES

Table 1

Subject Number	Product No. "B"
01	3.75
03	3.00
04	3.00
05	3.00
14	3.00
15	2.40
16	3.75
19	3.00

Mean=	3.11
SD=	0.44
SE=	0.16
5% MEAN=	0.16
N=8	

Table 2

Subject Number	Product No. "C"
01	5.00
03	5.00
05	4.00
08	5.00
13	5.00
15	4.00
16	6.25
21	5.00

Mean=	4.91
SD=	0.71
SE=	0.25
5% MEAN=	0.25
N=8	

Table 3

Subject Number	Product No. "D"*
02	>7.51
04	9.37
07	7.51
08	6.00
13	9.38
17	>9.39
18	9.39
19	6.00
20	6.00
22	6.00

Mean=	7.46
SD=	1.67
SE=	0.59
5% MEAN=	0.37
N=8	

*>= Total protection at all irradiated product sites, greater than expected PFA result.

Table 4

Subject Number	Product No. "E" *
02	1.28
03	1.60
04	<1.60
05	<1.28
06	1.60
13	2.00
15	1.60
16	2.50
17	1.20
22	1.60

Mean=	1.67
SD=	0.41
SE=	0.14
5% MEAN=	0.08
N=8	

*< = No protection at all irradiated product sites, less than expected PFA results.

Table 5

Subject Number	Product No. "F"
01	2.50
02	2.00
04	2.00
05	2.00
13	2.50
17	3.13
18	3.13
19	2.00

Mean=	2.41
SD=	0.50
SE=	0.18
5% MEAN=	0.12
N=8	

Table 6

Subject Number	Product No. "G"
01	3.00
02	2.40
03	2.40
04	3.75
14	4.69
15	4.69
20	3.00
21	3.00

Mean=	3.37
SD=	0.92
SE=	0.33
5% MEAN=	0.17
N=8	

Table 7

Subject Number	Product No. "I"
06	2.00
07	1.60
08	2.50
09	2.00
14	2.50
17	2.50
18	3.13
20	2.00

Mean=	2.28
SD=	0.47
SE=	0.17
5% MEAN=	0.11
N=8	

Subject Number	Product No. "J" *
08	4.00
09	<2.40
10	<2.40
11	<2.40
14	3.91
16	3.91
18	2.50
19	2.50
20	2.50
21	2.50
22	1.60

Mean=	2.93
SD=	0.89
SE=	0.31
5% MEAN=	0.15
N=8	

*< = No protection at all irradiated product sites, less than expected PFA results.

APPENDIX II

CLINICAL MATERIAL RECORD

TKL RESEARCH, INC. 4 FOREST AVENUE PARAMUS, NJ 07652

CLINICAL MATERIAL RECORD

Study No.: PB8404000

PRODUCT ID CODE	PRODUCT DESCRIPTION	EXPIRATION DATE	RECEIPT	ADDITIONAL RECEIPT	STORAGE CONDITIONS *see code below	RETAINED SAMPLE
CODE B MF# SWS316-074	OFF WHITE LOTION	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A
CODE C MF# SWS316-076	OFF WHITE LOTION	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A
CODE D MF# SWS316-078	OFF WHITE LOTION	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A
CODE E MF# SWS316-094	WHITE LOTION	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A
CODE F MF# SWS316-096	WHITE LOTION	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A
CODE G MF# SWS316-095	WHITE LOTION	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A
CODE I MF# BCS541-116	WHITE LOTION	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A
CODE J MF# BCS541-118	YELLOWISH LIQUID	02/01/01	DATE: 3/31/2000 AMOUNT: 2 X 80g	N/A	A	N/A

DISPOSITION DATE: To be discarded 8/28/00 CARRIER: _____

DISPOSITION: ❻ RETURNED ❻ DISCARDED

SPONSOR: The Procter & Gamble Company

RECEIPT RECORDED BY: TMT

DISPOSITION RECORDED BY: _____

LOG BOOK PAGE NUMBER: 135

*STORAGE CONDITIONS: A = AMBIENT (Room Temperature) CONDITIONS W = WARMER (Temp. Req._____) R = REFRIGERATED (4-8°C) F = FROZEN (Temp. Req._____)

O = OTHER (EXPLAIN): _____

STORAGE INFORMATION: An aliquot of the sample or a full (pre-packaged) product or device will be retained for a period of six months.

APPENDIX III

DEMOGRAPHICS

KEY:

F = Female
M = Male

DEMOGRAPHICS

Entry No.	Subject No.	Sex	Race	Age
01	51892	F	WHITE	48
02	12896	F	WHITE	40
03	15784	F	WHITE	40
04	58366	F	HISPANIC	39
05	50253	M	ASIAN	28
06	47484	F	ASIAN	25
07	50690	F	WHITE	60
08	16801	F	WHITE	64
09	49869	F	WHITE	49
10	47783	F	WHITE	42
11	45755	F	WHITE	56
12	41331	F	WHITE	49
13	48169	F	WHITE	60
14	59391	F	WHITE	59
15	66551	F	WHITE	42
16	17689	F	WHITE	58
17	19486	F	WHITE	46
18	13253	F	WHITE	64
19	47856	F	WHITE	45
20	61261	F	HISPANIC	42
21	07168	F	WHITE	56
22	53792	F	WHITE	35

DISTRIBUTION OF AGES

Under 18	: n =	0
18 to 25	: n =	1
26 to 35	: n =	2
36 to 45	: n =	7
46 to 55	: n =	4
56 to 65	: n =	8
Over 65	: n =	0
Total	: n =	22

Mean Age: 47.6

Age range for the study: 25 to 64

APPENDIX IV

INFORMED CONSENT DOCUMENT

INFORMED CONSENT
ULTRAVIOLET A FACTOR DETERMINATION

STUDY NO.:PB840400

PURPOSE: The purpose of this research is to determine the ability of sunscreen products to prevent the sun-tanning or sun burning reaction caused by the ultraviolet A (UVA) portion of sunlight when contact with the skin is followed by UVA light exposure and to determine the UVA protection factor of the sunscreen products.

ELIGIBILITY: A member of the research staff will explain the study to you and you will be asked to read and sign this consent form. You will be asked to complete a form about your medical history and a member of the research staff will examine your back.

Only healthy volunteers with normal skin will be allowed to participate in this study.

While you are in this study, please inform the clinical staff if you have any change in your medical health, as well as any medications you are taking or applying to your skin. This includes medication ordered for you by another doctor, or drugs you buy from a store without a prescription. You may not participate in any other study while you are a subject in this study.

If you are a female of childbearing potential (i.e., not surgically sterile or have not experienced menopause), you must agree to prevent pregnancy throughout this three-day study by using an accepted form of birth control [e.g., oral contraceptive pill, IUD, condom/diaphragm with spermicide, abstinence (no sexual relations)]. Pregnant women and nursing women are excluded from this study. Women should not become pregnant or breast-feed an infant while participating in this study to prevent any unknown risk to the unborn or nursing child.

STUDY PROCEDURE: Upon qualifying, you will be expected to discontinue use of all creams, lotions, moisturizers, or any other skin products on your lower back and to protect your back from sun exposure for the duration of the study. You will take part in a study that extends over a 3 day period. A minimum of 10 subjects will participate in this research study.

A small portion of your lower back will be exposed to UVA light from a solar simulator (a lamp whose light is similar to that of sunlight but more intense). You will be exposed at six (6) sites which are circular and have a diameter of one (1) centimeter (less than 2 inches). This is done to see the least amount of light it takes to produce a sun tan reaction on the skin. The exposure will be approximately 15 minutes. You will return the next day to have the sites evaluated.

On day two up to five other areas of your back (each about the size of a business card) will have sunscreen products applied and exposed to UVA from a solar simulator. The exposures will be approximately 14-60 minutes at each site. You may wish to bring reading material for this visit.

The following day you will return to the study center to have the study sites evaluated for a tanning or redness response. You will be required to remain at TKL Research for approximately 10 minutes.

POSSIBLE DISCOMFORTS OR RISKS: There may be some irritation at the study sites similar to a sunburn and/or a suntan, or in rare cases, a reaction at the study sites where the test formulation touches the skin, characterized by varying degrees of redness, swelling, blistering, temporary stinging, burning sensation, itching, eczema (inflammation, scaling and itching), petechiae (small pinpoint non-raised red dots), dryness, hyperpigmentation (darkening of the skin) and/or peeling. Occasionally, a reaction may result in localized lightening or darkening of the skin, which may persist for several weeks or months before fading. The Study Coordinator and/or Investigator (the Study doctor) may withdraw you from this study for reasons of, but not limited to, a severe reaction, an illness, or your failure to follow directions.

You will be told of any significant new findings developed during the course of this study which may relate to your

INFORMED CONSENT
ULTRAVIOLET A FACTOR DETERMINATION

STUDY NO.:PB840400

COMPENSATION: In the event that any injury should occur to you as a direct result of the test materials and your participation in this study, appropriate medical treatment will be provided by TKL Research, Inc. paid by the Sponsor (the company conducting this study). If such reactions occur, TKL personnel should be contacted immediately at (201) 587-0505 including nights and weekends.

VOLUNTARY PARTICIPATION: Participation in this study is voluntary. You may refuse to participate or withdraw at any time without prejudice or loss of benefits that you would otherwise be entitled. There are no anticipated costs to you that may result from your participation in this study.

FINANCIAL INCENTIVE: You will be paid $70.00 upon completion of all phases of this study. If, in the judgment of the investigating personnel, it is best to discontinue your participation in this study, due to an adverse experience or severe reaction, you will be paid in full for your participation. If you are dismissed for refusal to obey rules or follow instructions you will not be paid. If you drop out on your own accord for personal reasons beyond your control you will be paid proportionately.

BENEFITS/ ALTERNATIVES: There is no personal benefit to participating in this study. Not participating in this study is your alternative.

RELEASE OF MEDICAL RECORDS AND CONFIDENTIALITY: Unless required by law, only the investigator (study doctor), the sponsor (the company conducting this study), employees of TKL Research, Inc. and representatives of the Essex Institutional Review Board (a committee that has reviewed this research project to help ensure that the rights and welfare of the participants are protected and that the study is carried out in an ethical manner) and government regulatory agencies will have access to confidential data which identifies you by name. You will not be identified by name in any reports or publications resulting from the study.

WHOM TO CONTACT: If you have additional questions about this research during the course of the study or in the event of a research-related injury or any other problems, call Alan H. Greenspan, MD, Principal Investigator, or Maureen Damstra, Clinical Research Coordinator, at (201) 587-0505. You may contact the Essex Institutional Review Board, 121 Main St., Lebanon, NJ 08833, (908) 236-7735 if you have a question about your rights as a research subject.

CONSENT

I have read and understand this consent form. I have had an opportunity to ask questions and my questions have been answered. I voluntarily consent to participate. I will be given a copy of this signed consent form. By signing this form I have not given up any of my legal rights which I may have in the case of negligence or other legal fault of anyone who is involved in this study that I would otherwise have as a research subject.

SIGNATURE

SUBJECT: _____ _____ _____
Signature Please Print Date

WITNESS: _____ _____ _____
Signature Please Print Date

Entry No:_____

APPENDIX V

PROTOCOL

PROTOCOL FOR

DETERMINATION OF STATIC UVA PROTECTION FACTORS (PFA)

TKL-8401-M

SUBMITTED BY:

The Procter & Gamble Company
Sharon Woods Technical Center
11511 Reed Hartman Highway
Cincinnati, OH 45241-9974

SUBMITTED BY:

TKL Research, Inc.
4 Forest Avenue
Paramus, NJ 07652

Date

March 29, 2000

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1.0 TITLE

Determination of Static UVA Protection Factors (PFA)

2.0 OBJECTIVE

The objective of the study is to determine the static UVA Protection Factor (PFA) for Sunscreen formulas.

3.0 STUDY DESIGN

This will be a controlled, randomized study. Subjects entered into the study will have their initials entered sequentially on the Subject Assignment Sheet. The randomization of the application of the study products to the areas of the subject's back will be indicated on this sheet.

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Each subject is expected to participate in the study for 3 days.

3.1.1 Inclusion Criteria

1. Individuals 18-65 years old will be enrolled into the study only after it is determined that each belongs to skin type I, II, or III as defined in the proposed monograph for SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN DRUGS, Federal Register of August 25, 1978 (43FR38206-38269).

2. Individuals free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, will interfere with the study results or increase the risk of adverse events.

3. Individuals who complete a photo study Medical Screening form, as well as a Medical/Personal History form.

4. Individuals who read, understand and sign an informed consent agreement.

3.1.2 Exclusion Criteria

1. Medical history not consistent with good general health.

2. History of recent (topical or systemic) use of medication, cosmetic, soap, or fragrance formulations known to product abnormal sunlight responses.

3. History of severe abnormal responses to sunlight.

4. Individuals with any visible skin disease, excessive hair, blemished, tan or uneven pigmentation at the study site which, in the opinion of the investigative personnel will interfere with the study results.

5. History of chronic use of high doses of antihistamine or anti-inflammatory medications (e.g., aspirin, ibuprofen or corticosteroids) or current use of any antihistamine, NSAID or prescription anti-inflammatory drugs.

6. Individuals taking medication suspected of causing photobiological reactions (e.g. tetracyclines, thiazides).

7. Individuals with psoriasis and/or active atopic dermatitis /eczema.

8. Females who are pregnant, plan to become pregnant during the study, or are breast-feeding a child.

9. Individuals with diabetes, Addison's disease or thyroid conditions.

10. Individuals who are currently under steroidal treatment for astham, non steroidal treatment is acceptable (e.g., Proventil inhaler).

11. Individuals with cataracts.

12. Individuals with a history of skin cancer.

13. Individuals with a history of hepatitis.

14. Individuals with a known sensitivity to cosmentics, skin care products or topical drugs as related to product(s) being evaluated.

4.0 PROCEDURE

4.1 PRE-STUDY

Before being entered into the study, the subjects will be pre-screened by the investigator for the criteria indicated in the Subject Selection section. Only subjects who meet the requirements of this section, have signed an informed consent according to 21 CFR, Part 50 and have given an appropriate medical history will be entered into this study.

4.2 LIGHT SOURCE

The source of radiation will be a Xenon arc solar simulator having a continuous emission spectrum in the UVA (320 to 380 nm) region with less than 1% of its total energy contributed by wavelengths below 320 nm. The lamp will be filtered with a WG335 filter, 3mm in thickness or equivalent. There will be less than 2% of erythemal effectiveness of the source contributed from wavelengths lower than 320 nm, and no more than 10% of the total output of the lamp will be visible and infrared radiation. The maximum intensity at the point of the skin exposure must be less than 150 mW/cm^2 total irradiance, as measured by a calibrated thermopile.

4.3 MINIMAL RESPONSE DOSE (MRD) DETERMINATION

On Day 1 of the study, a minimal response dose (MRD) for unprotected skin will be determined for each subject by irradiating 5 one-centimeter subsites on the lower back. The dose interval selected for the irradiation of the subsites shall be a geometric series wherein each exposure dose interval is 25% greater than the previous exposure. This geometric series is represented by 1.25 X n where n is the previous exposure dose.

For subjects of unknown sensitivity, the dose series will be in the range of 10 to $31J/cm^2$. For subjects with predetermined UVA MRD values, the dose series will be centered around the previously determined MRD.

After the exposure is completed, all immediate responses will be recorded. These include immediate darkening or tanning, immediate erythema, whealing, edema or flaring at the irradiation site. Subjects exhibiting the last three responses will be disqualified from the study procedures.

After the immediate responses are recorded, the subjects will be instructed to shield the exposed areas from further UV exposure. Sixteen to 24 hours after the UV exposure, the 5 subsites will be graded using the scale indicated in the Clinical Measurements section. The subsite with the lowest exposure dose showing a minimally perceptible tanning or erythema response will be selected as the MRD. The unprotected MRD will be reconfirmed on the day the test products are evalauted.

4.4 PFA Determination

1. Application of Test Products: Using a permanent marker, each subject will have six 50cm^2 test areas drawn on the back between the beltline and the shoulder blades and lateral to the midline. Five of four test areas will be for the study products and the remaining one will be used for the MRD. Following the randomization indicated on the Subject Assignment Sheet, 100 mg of Sunscreen formula will be applied to the appropriate test area and spread over the entire area using a finger cot.

   In the same manner, 100 mg of Sunscreen formulas will be applied to the designated test areas. The test areas are allowed to dry for 20 minutes. During this period, the subjects should be instructed not to touch their backs against any surface.

2. Irradiation of the Static PFA Test Areas: While the test areas are drying, the solar simulator exposure doses required for Sunscreen formulas will be calculated based on the MRD of the subject and the expected PFA value of the sunscreen.

   Each 50cm^2 test are will contain 5 subsites that will be irradiated. The dose intervals selected for the subsites shall be a geometric series in which each exposure doe (subsite) is 25% greater than the previous exposure dose (1.25 x n). For example, if the subject's unprotected MRD is 10 J/cm^2 and the expected PFA of the sunscreen is 2, then the central exposure interval (third subsite) will be 10 X 2 or 20 J/cm^2, respectively. At the completion of the exposure at each subsite.

   Sixteen to 24 hours after irradiation, all subsites in the test areas will be graded for responses using the scale indicted in the Clinical Measurements section and the PFA values will be determined.

5.0 CLINICAL MEASUREMENT

Sixteen to 24 hours after irradiation, all subsites in the test areas will be graded for responses using the scale indicated below. The person performing the grading will be unaware of the identity of the treatments applied to the test areas.

0	=	No reaction
0.5	=	Minimal tanning or erythema, barely perceptible
1	=	Light brown or red color with definite borders
1.5	=	Medium brown or red, well-defined
2	=	Dark brown or red with edema

The lowest dose subsite showing a minimally perceptible response (0.5) will be selected as the MRD value. The PFA of the sunscreen is the ratio of the exposure dose for the protected MRD divided by the dose for the unprotected MRD (PFA = protected MRD/unprotected MRD).

6.0 MATERIALS

6.1 ADMINISTRATION

On the day of study, a research technician will weigh the test articles and then apply by manually and uniformly spreading the test article over a 50 cm^2 area at a dose of 2mg/cm^2. A waiting period of at least 15 minutes is required before proceeding with the ultraviolet exposure.

6.2 SUPPLIES

All study materials will be shipped by the sponsor will explicit instructions for handing and storage. Upon receipt all products will be logged in and stored in a secure area.

7.0 ADVERSE EVENTS

An adverse event is defined as an occurrence of a new symptom(s) of a medical nature during use of the study material whether or not considered related to the study material, e.g., headache, influenza, broken bones, fever, nausea, etc. All clinical adverse events, whether observed by the clinical staff or by the subject and whether or not thought to be study-related, are considered adverse events and will be recorded on an Adverse Event form. Assessment of severity and causality will be based on definitions found on the Adverse Events report form. A separate Adverse Event Form will be completed for each adverse event reported.

Serious adverse events will be reported to the Sponsor within 24 hours of the Investigator's knowledge of the event. Clinical personnel will contact the Sponsor as soon as the adverse event is identified.

It is understood that the Investigator will stop application of the study material at any time the Investigator feels the subject's condition so indicates.

8.0 CONCOMITANT MEDICATIONS

The use of concomitant medications will be allowed only if it had been detrmined that the medication will not in any way interfere with the study results.

9.0 INTERCURRENT ILLNESS

Any intercurrent illness occurring during the course of this study should be recorded in the case report form.

10. DISCONTINUATION FROM THE STUDY

Patients must be discontinued from the study for the following reasons:

Serious or intolerable adverse experiences at least possible related to study treatment in the judgment of the Investigator.

Requirement of prohibited concomitant medication as outlied in the ecxlusion criteria and concomitant medications.

Non-compliance by the subject.

Withdrawal of consent by the subject.

For all subjects discontinued from the study, the reason for the discontinuation will be documented in the Case Report Form.

11.0 STATISTICAL ANALYSIS

Statistical Analysis – The following calculations for each of the products will be performed:

Mean Static PFA
Standard Deviation
Standard Error
5% of the Mean

Rejection of Data – Test data will be rejected if the exposure series fails to elicit an MRD on treated or unprotected skin sited. Test data will be rejected if the responses on the treated sited are randomly absent, or if the subject was noncompliant.

12.0 STUDY MONITORING AND RECORD RETENTION

12.1 QUALITY ASSURANCE

All data and supporting documentation for this study will be audited by the TKL Quality Assurance Department and deemed to be accurate, complete and in compliance with all requirements of the protocol and TKL's Standard Operating Procedures.

12.2 FINAL REPORT

At the conclusion of the study, the Sponsor will receive a final report including background data, study materials, tables of raw data and data summary, and an interpretation with discussion, if required, of results.

12.3 AGREEMENT WITH PROTOCOL

TKL Research, Inc. agrees to conduct the title study as provided in this protocol, in accordance with all government regulations and to make no changes without prior notification to the Sponsor except where a modification is deemed necessary to eliminate or reduce risk to human subjects.

SUBMITTED BY:

_____ _____

Maureen Damstra
Clinical Research Coordinator
TKL Research, Inc.

Date

APPROVED BY:

_____ _____

J Frank Nash, Ph. D.,
Senior Scientist
The Procter & Gamble Company

Date

From: J Frank Nash
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TO:

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